

What is claimed is:

1. A method for determining a disease state of a subject comprising;  
obtaining a biological sample containing protein from said subject,  
measuring levels of protein markers of the disease state in said sample, and  
comparing the levels of said markers to the levels of the same markers in a control sample from a subject not having the disease state or a control standard.
2. The method of claim 1 wherein the protein markers are selected from the group consisting of the markers in Tables 1-5.
3. The method of claim 2 wherein the protein markers are selected from the group consisting of the markers for the conditions of obesity, osteoporosis, diabetes, osteoarthritis or hypertension.
4. The method of claim 1 wherein said disease state is selected from the group consisting of obesity, osteoporosis, diabetes, osteoarthritis and hypertension.
5. The method of claim 1 wherein the levels of protein markers determines the relative severity of the disease state.
6. The method of claim 1 further comprising;  
measuring levels of individual proteins in a proteome of said biological sample from the subject,

comparing these levels with levels of the same proteins in the proteome from a sample from a control subject or a control standard, and

detecting which proteins are increased or decreased by a statistically significant amount

wherein the proteins so detected are the markers for the disease state.

7. The method of claim 6 wherein the statistically significant amount is determined as a  $p < 0.01$ .

8. The method of claim 7 wherein  $p < 0.001$ .

9. The method of claim 6 wherein said disease state is selected from the group consisting of obesity, osteoporosis, diabetes, osteoarthritis and hypertension.

10. The method of claim 6 wherein said proteome is prepared by two-dimensional electrophoresis.

11. A protein marker selected from the proteins of Tables 1-5.

12. A protein marker of claim 11 selected from the proteins are markers for the diseases of obesity, osteoporosis, diabetes, osteoarthritis or hypertension.

13. A binding reagent bound to a detectable label specific for a protein selected from the group consisting of protein markers of claim 11.

14. A binding reagent bound to a detectable label specific for a protein selected from the group consisting of protein markers of claim 11.

15. A method of monitoring efficacy of a therapy for a disease state in a subject comprising;

obtaining a biological sample containing protein from said subject,

measuring levels of protein markers of the disease state in said sample, and

comparing the levels of said markers to the levels of the same markers in the same subject at a previous time.

16. The method of claim 15 wherein the disease state is selected from the group consisting of obesity, osteoporosis, diabetes, osteoarthritis and hypertension.

17. A protein selected from the group consisting of proteins listed in Tables 1-5.

18. A protein according to claim 17 in isolated form.

19. A binding reagent specific for the protein of claim 17.

20. The binding reagent of claim 19 bound to a detectable label.

21. A method for screening candidate compounds biological activity against obesity, osteoporosis, diabetes, osteoarthritis or hypertension comprising;

contacting a candidate compound with a subject having obesity, osteoporosis, diabetes, osteoarthritis or hypertension, measuring the level of a protein marker of Tables 1-5, and comparing the level of protein marker to the level of protein marker in a control sample from a subject not having the disease state or a control standard.

22. A pharmaceutical composition comprising;  
a modifier of the level of or the activity of a protein marker of Tables 1-5, and  
a pharmaceutically acceptable carrier,  
wherein said modifier was identified by the process of claim 21.

23. The pharmaceutical composition of claim 22, wherein the modifier is in an effective amount for treating obesity, osteoporosis, diabetes, osteoarthritis or hypertension.

24. A method for treating a disease state comprising;  
administering an effective amount of a modifier of the level of or the activity of a protein marker of Tables 1-5, and  
a pharmaceutically acceptable carrier,  
wherein said modifier was identified by the process of claim 21.

25. The method of claim 24, wherein the modifier is in an effective amount for treating obesity, osteoporosis, diabetes, osteoarthritis or hypertension.

26. A method for screening candidate compounds for detection or therapeutic activity against a disease state comprising;

contacting a candidate compound with a protein marker of Tables 1-5,

measuring the activity of said protein marker or the binding of said compound to said protein marker, and

selecting for further development those compounds which affect activity or bind.

27. A method of identifying biological pathways involved in a disease state, comprising;

a) obtaining a biological sample from a subject having obesity, osteoporosis, diabetes, osteoarthritis or hypertension,

b) determining levels of proteins in the proteome in said biological sample,

c) comparing the levels of each protein in said proteome to levels of protein in a control sample from a subject not having the disease state or a control standard,

d) determining which proteins have statistically significantly higher or lower levels in each sample,

e) identifying a plurality of the determined proteins, and

f) deducing which biological pathways are affected based on the identities of said proteins,

wherein said biological pathways contain at least one protein having a statistically significantly higher or lower level in a comparison between the two samples.

28. The method of 27 wherein one sample has a combination of two or more protein markers which have statistically

significantly higher or lower levels than the same combination of protein markers in the other sample.

29. A standardized two-dimensional electrophoretic distribution of proteins from a biological sample from a subject having obesity, osteoporosis, diabetes, osteoarthritis or hypertension.

30. The standardized two-dimensional electrophoretic distributions of proteins according to claim 29 wherein the biological sample is human serum.

31. The standardized two-dimensional electrophoretic distribution of proteins of claim 29 wherein said subject is being treated with pharmaceuticals indicated for the same conditions.

32. The method according to claim 15 wherein the proteome of the biological sample is measured.

33. The method according to claim 23 wherein the proteome of the biological sample is measured.

34. The method according to claim 26 wherein the disease state is obesity, osteoporosis, diabetes, osteoarthritis or hypertension.

35. A method for determining whether a combination of proteins together form a protein marker of a disease state when

the proteins individually are not markers with a desired level of statistical significance, comprising;

determining proteins that are at altered levels in biological samples from a subject having the disease state and controls or biological samples from a subject without the disease state, which proteins are less than the desired level for statistically significant markers by themselves,

selecting two or more of said proteins,

combining the values for two or more of said proteins and determining whether the combination of values is altered in a statistically significant manner,

wherein said combination of proteins results in the desired level of statistically significant differences between biological samples from subjects with the disease state and controls or biological samples from a subject without the disease state.

36. The method of claim 35 wherein said disease state is obesity, osteoporosis, diabetes, osteoarthritis or hypertension.

37. A composition comprising the combination of proteins of claim 36 forming the protein marker.

38. A set of binding reagents, wherein a binding reagent specifically binds to each different protein in the composition of claim 37.

39. A method for finding drug development targets for obesity, osteoporosis, diabetes, osteoarthritis or hypertension comprising;

measuring the level of each protein in a proteome of a biological sample containing protein from a subject having obesity, osteoporosis, diabetes, osteoarthritis or hypertension, comparing the level of each protein to the level in a control biological sample,

determining which proteins are found in a statistically significant abnormal amount thereby indicating them to be protein markers, and

determining which of the protein markers is involved in the same metabolic pathway as said disease state, thereby indicating these to be drug development targets.

40. Drug development targets determined by the method of claim 39.

41. A binding reagent specific for the drug development targets of claim 39.

42. The binding reagent of claim 41 bound to a detectable label.

43. The drug development targets of claim 40 selected from those of Tables 1-5.

44. The drug development targets of claim 43 for the diseases of obesity, osteoporosis, diabetes, osteoarthritis or hypertension.

45. A method for determining whether a protein is a protein marker of a disease state when the protein is not a statistically significant marker comprising;

a) determining protein markers for a disease state and protein submarkers that have an altered level but are altered to less than a statistically significant amount by themselves, and

b) comparing the level and direction of change of protein markers with the protein submarkers,

wherein protein submarkers that are altered in tandem consistently with protein markers in level and direction or opposite direction are themselves considered protein markers.

46. A protein submarker produced by the method of claim 45.

47. A binding reagent specific for a protein submarker of claim 45.

48. A method for generating an index marker for a particular physiological state comprising;

determining protein markers that differ in a statistically significant manner between biological samples from a subject with a disease state and a control biological sample, which proteins are statistically significant protein markers by themselves,

selecting two or more of said protein markers,

combining the values for two or more of said protein markers and determining whether the combination of values is altered in a manner of greater statistical significance.

49. An index marker determined by the process of claim 48.

50. A method for cloning a gene encoding a protein in Tables 1-5 comprising,

determining at least a partial amino acid sequence of said protein,

deducing a nucleotide sequence for a gene encoding said protein, and

isolating or synthesizing a gene encoding said nucleotide sequence.

51. The gene for a protein in Tables 1-5 produced by the process of claim 50.

52. An antisense compound capable of inhibiting expression of the gene of claim 51.

53. A method for determining whether plural agents act in an additive or synergistic manner comprising;

exposing a subject to a first agent and obtaining a protein containing biological sample thereof,

exposing a subject to a second agent and obtaining a protein containing biological sample thereof,

exposing a subject to a first agent and a second agent and obtaining a protein containing biological sample thereof,

measuring the levels of protein markers in each biological sample,

comparing the changes in levels of protein markers between a subject exposed to a first agent, a subject exposed to a second agent and a subject exposed to a first and second agent and

determining whether the effects of said first agent and said second agent are cumulative or synergistic.

54. A pharmaceutical composition comprising said first agent and said second agent when the effects are more than additive as determined by the method of claim 53.

55. The method of claim 53 wherein said markers are selected from those of Tables 1-5.